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Editorial

Aztreonam for inhalation solution, challenges to drug approval and integration into CF care

Many new therapies are emerging for the treatment of CF. In the last 2 years, six agents have been approved by the Food and Drug Administration (FDA) and four agents have given an opinion in favor of granting a marketing authorization by the European Medicines Agency (EMA) representing dramatic results from decades of investment in basic and clinical science. In this month's journal, Assael and colleagues [13] present data from a phase 3 open-label, randomized, parallel-group, active-comparator non-inferiority trial comparing aztreonam for inhalation solution (AZLI) and inhaled tobramycin nebulizer solution (TNS). They concluded that AZLI demonstrated statistical superiority in lung function and reduced acute pulmonary exacerbations compared to TNS. This trial raises some key issues in CF drug development. First, the role of non-inferiority design strategies pose unique limitations. Second, major regulatory bodies (FDA and EMA) are not necessarily in alignment about non-inferiority trials. Third, these new agents are very costly, adding considerably to treatment costs.

Using an interesting design element this study included co-primary endpoints: non-inferiority of AZLI for relative change from baseline in FEV_1% predicted at Day 28 and superiority of AZLI for actual change from baseline in FEV_1% predicted compared to TNS across 3 treatment cycles [13]. Non-inferiority trial design is an increasingly common study design allowing comparison of a new therapy to an existing standard therapy (active comparator studies). Another option is to conduct an equivalence study — equivalence is established when clinically important differences favoring standard care are ruled out [1]. These two study formats are often employed when one has two agents (same indication), with the newer agent having reduced toxicity profile or easier administration. Of these designs, non-inferiority studies have become the dominant design. A non-inferiority study is essentially a one sided test of equivalence; the design will determine if new treatment is worse by less than the non-inferiority margin which is pre-specified [2]. A key challenge is deciding a priori the non-inferiority margin. Assael and colleagues [13], set the non-inferiority margin (non-inferiority primary aim) at 4%, meaning if the 95% confidence interval lower boundary for the treatment difference (AZLI–TNS) was >-4%, AZLI would be deemed non-inferior to TNS. This margin should be determined on clinical grounds and published literature and will profoundly affect sample size. Publication bias (not publishing negative trials) can complicate the establishment of appropriate non-inferior margins. The other significant challenge to non-inferiority and equivalence studies [2,3], is investigators cannot confirm that active control is still effective (the constancy assumption). The literature notes examples of waning of efficacy of approved medications over time; an example includes antidepressants (nomifensine vs imipramine) [4,5]. "Biocreep" occurs when non-inferiority sequential comparisons are done in the setting of waning efficacy of older medications [2,3]. Thus if TNS efficacy has diminished, stating that the new therapy is no more than 4% FEV_1% predicted worse could mean that the new agent is ineffective and even potentially harmful. This study and one prior study provide data to suggest the efficacy of TNS has diminished; FEV_1% predicted changed by only +0.55% after 28 days of TNS [13] in the current study and only +1% (95% CI: −1.2 to 3.7) in another recent study [6]. This is one reason why non-inferiority studies may concern some regulatory bodies. The current study was fortunate to not only show non-inferiority of AZLI over TNS, but also demonstrated superiority over TNS at study completion with a treatment difference (AZLI–TNS) of 3.4% ($p=0.02$).

There are clear challenges to drug development for CF. The EMA requests the following for drug development: randomized active-controlled trials are mandatory with the requirement of superiority with active control for mucolytic agents [7]. Blinding is desired when feasible [7]. The FDA prefers two superiority blinded placebo-controlled randomized trials. While the FDA accepts equivalence and non-inferiority, they can have no more than 10% inferiority margin and should demonstrate that 'test' treatment is effective or efficacious (would have beaten placebo) [4,5,8,9]. These differences between study design recommendations can complicate and add to the expense of drug development in orphan diseases like CF; the AZLI program conducted three phase 3 clinical trials towards regulatory approval.

After agency approval, will health care systems be able to deliver new drugs? The FDA and EMA approve new therapies in the USA and in the European Union (EU) and influence decisions by other independent national agencies. The

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subsequent decision about funding new treatments follows and in Europe is coordinated nationally. Funding of new therapies varies considerably between countries even those within the EU and in some cases within countries. This is particularly the case where funding of health is split between different government jurisdictions (e.g. Canada and Australia) or between private medical insurance providers and government funding organizations (e.g. USA). While, the FDA and EMA approved TNS in 1997, its availability has been delayed in some parts of the world. In Australia, the Therapeutic Goods Administration approved TNS is early 2000, however IV tobramycin preparations continued to be used during the decade until funding by the government in 2011. Similarly, TNS has been available in some Canadian provinces but in others IV solution continues to be used, as it is in New Zealand.

AZLI has been approved by the FDA and EMA and is currently available and funded in ~50% of EU countries and a decision pending in others. Given its likely cost, its availability is likely to be delayed in many parts of the world. In most western European countries (including non-EU) out of pocket expenses for CF therapies are relative small. For example, in Italy all CF therapies are provided free of charge to the patient with the Italian government paying the full cost. Similar, systems operate in Scandinavia and Spain. In The Netherlands, costs are paid by health insurance companies and membership is compulsory, though if one is not working the premium is paid by the government.

Funding models for CF care including drug therapy may contribute to considerable variability in health care outcomes and are likely to be a factor in poorer outcomes in patients from Eastern Europe and those living in parts of the world where funding for or access to health care is limited [10]. As many new therapies are undergoing intense investigation, the drug cost component of CF care is likely to increase in the coming years and may contribute to further differences between outcomes internationally. The current cost of ivacaftor is very likely to be prohibitive in many other parts of the world. Similar challenges and some early solutions have been seen in other diseases states (e.g. antiretroviral treatment for HIV infection) which are expensive and affect large populations in the developed and developing worlds [11,12]. Learning from other disease experiences will be important, as many new CF therapies are likely to be submitted from approval in the coming years.

Conflict of interest disclosures

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